

TAB A

Bcl-2 ANTISENSE PROTOCOLS BEFORE THE 09/709,170 APPLICATION PRIORITY DATE

April 26, 2006

AUTHOR	DATE	ROUTE	DAYS	COMMENTS
Webb	1997 ASCO (1997 Lancet)	SC Infusion (daily w/ portable syringe driver)	14	bcl-2 protein levels measured at start of treatment; 2 weeks and 6 weeks. One patient was apparently assayed at 7 days as well (#6, Fig. 2), and had stable disease at week 6 (pg. 1139, tumor response). Patient 2 also had a decrease in bcl-2 protein and stable disease. 8 of 9 patients had stable disease or progressive disease on the study (little or no therapeutic benefit). A correlation between bcl-2 reduction and tumor response is not disclosed or suggested.
Morris	1999 ASCO	IV Infusion	14	Patient bcl-2 levels not reported.
Waters	1999 ASCO	SC Infusion	14	bcl-2 protein levels measured in tumor samples of 13 patients, and after treatment was reduced in 5 patients. Contains no disclosure suggesting a correlation between bcl-2 reduction and tumor response.
Jansen	1999 ASCO	IV Infusion	14	Reduction in bcl-2 protein levels coincident with therapy. Contains no disclosure suggesting a correlation between bcl-2 reduction and tumor response.
Scher	2000 ASCO	Cont. Infusion	14-21	At 4.1 mg/kg/d, bcl-2 protein expression decreased within one week, peak effect at 8-15 days. Conclusion: G3139 can decrease bcl-2 protein expression. Contains no disclosure suggesting a correlation between bcl-2 reduction and tumor response.
Chen	2000 ASCO	Cont. Infusion	21	bcl-2 downregulation at doses ≥ 2 mg/kg/day. At 3 mg/kg/d, maximum bcl-2 reduction seen by day 3 of infusion. Tumor response observed in 2 patients. Contains no disclosure suggesting a correlation between bcl-2 reduction and tumor response.
Chi	2000 ASCO 2001 Clin Cancer Res	Cont. IV Infusion	14	bcl-2 expression evaluated, no disclosure of results in abstract. Journal disclosure: bcl-2 protein reduced in 5 of 5 patients at 5 mg/kg/d at day 8. Patient 23 had >50% reduction in PSA, described as a good therapeutic response, but had only 10% reduction in bcl-2 levels (Fig. 1 and Fig. 2). Compare Patients 20 & 24 with 25-50% reduction in bcl-2 (Fig. 2), but who are not listed among those having a tumor response.

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Waters	2000 J. Clin. Oncol. (May)	SC Infusion	14	See Tables 4 & 5. Patient 20's reduction in bcl-2 was less than half that of Patient 19 (15% vs. 36%) but both had stable disease. Patient 12 (32%) had a bcl-2 reduction comparable to Patient 19 (36%) but had progressive disease rather than stable disease. The largest bcl-2 reduction was Patient 6 (47%), who only had a minor response. Of the three patients who had bcl-2 analysis at day 7, Patient 11 and Patient 12 had dramatically different therapeutic outcomes (stable disease vs. progressive disease) despite comparable reductions in bcl-2 expression (24% and 36% respectively). 9 of 21 patients had no change in bcl-2 levels in any tissue analysed. Demonstrates there is no reliable correlation between reduction in bcl-2 expression and tumor response.
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TAB B

BCL-2 ANTISENSE PROTOCOLS AFTER THE 09/709,170 APPLICATION PRIORITY DATE

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AUTHOR	DATE	ROUTE	DAYS	COMMENTS
de Bono	2001 ASCO	Cont. IV Infusion	5	Marked downregulation of bcl-2 by day 5. Contains no disclosure suggesting a correlation between downregulation of bcl-2 and tumor response.
Ochoa	2001 ASCO	Cont. IV Infusion	1-8	Marked downregulation of bcl-2 by day 6 at 5 mg/kg/d. Contains no disclosure suggesting a correlation between downregulation of bcl-2 and tumor response.
Jansen	2001 ASCO	Cont. IV Infusion	5	bcl-2 downregulated by day 4. Contains no disclosure suggesting a correlation between downregulation of bcl-2 and tumor response.
Morris	2002 Clin. Cancer Res.	Cont. Infusion	14 or 21	bcl-2 protein levels are shown for a single patient, and did not decline until day 15 of treatment. No major antitumor responses were observed - 37% had stable disease during treatment and 57% progressed (pg. 681, col. 2, "Clinical Effects"). "These studies are ongoing, as are determination of the association between clinical effects, dose and the timing and degree of bcl-2 protein reduction." (pg. 682, last sentence)
Rudin	2003 ASCO 2004 J Clin Oncol	Cont. IV Infusion	1-8	No evident suppression of bcl-2 in peripheral blood mononuclear cells on day 6 of treatment (pg. 1114, Analysis of bcl-2 Suppression...). These data are consistent with prior clinical reports (pg. 1115, first column - see Waters - J Clin Onc 2000 and Morris - Clin Cancer Res 2002, above; Chi - Clin Cancer Res 2001 and Marcucci - Blood 2003, below).
Demidov	2003 ASCO	Cont. IV Infusion	7	Analysis of bcl-2 levels not disclosed.
Esteva	2004 ASCO	Cont. Infusion	5	Analysis of bcl-2 levels not disclosed.
Marshall	2004 Ann Oncol	Cont. Infusion	21	Dose limiting toxicities prevented dose escalation beyond 4 mg/kg/day in 21 day infusion protocol. In 5 day infusion protocol even highest doses were tolerated without dose limiting toxicity. Shortened infusion had less cumulative toxicities and still allowed similar total delivery as the longer infusion.

Latest Priority Date of Genta Patent Application - 10 November 2000 - (Dark Line)
ASCO Annual Meetings are held in late May/early June

Conclusions:

Prolonged infusion was the standard protocol prior to Nov. 2000.
Following filing of the Genta patent application, the field quickly adopted the short infusion protocol of the invention because it allowed higher doses to be tolerated.

Treatment of cancer does not necessarily result from decreases in bcl-2 levels .

Therefore, observation of bcl-2 downregulation does not indicate cancer is inherently treated.